UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

	Application No.	Applicant(s)
Office Action Summary	09/844,544	ZENG ET AL.
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on <u>30 October 2007</u>.
2a)☐ This action is **FINAL**.　　2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) <u>15-26</u> is/are pending in the application.
　　4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) <u>15-26</u> is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
　　Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
　　Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
　　a)☐ All　b)☐ Some * c)☐ None of:
　　　1.☐ Certified copies of the priority documents have been received.
　　　2.☐ Certified copies of the priority documents have been received in Application No. _____.
　　　3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
　　* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO/SB/08)
　　Paper No(s)/Mail Date <u>12/19/07</u>.
4)☐ Interview Summary (PTO-413)
　　Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/07 has been entered.

Applicants response filed 10/30/07 is acknowledged and has been entered.

The Declaration of Dr. Samuel Strober, M.D. under 37 CFR 1.132 (filed 10/30/07) is acknowledged and has been entered.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir.1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method wherein the second therapeutic agent is an immunomodulating drug as recited in the instant claim.

The instant claim encompasses a method of treating SLE in a human comprising administering an anti-CD1d antibody that blocks the interaction of CD1d with a TCR and further comprises any immunomodulating drug. Except wherein the said immunomodulating drug is methotrexate, cyclosporine, chloroquine, hydroxychloroquine, azathioprine or cyclophosphamide, there is insufficient disclosure in the specification on such an immunomodulating drug.

The specification discloses at [0060] "Co-formulations: The subject CD1 blocking agent may be formulated or administered in conjunction with other agents that act to decrease polyclonal B cell activation or otherwise relieve the symptoms of SLE. These agents include non-steroidal anti-inflammatory drugs (NSAIDs), e.g. acetylsalicylic acid; ibuprofen; naproxen; indomethacin; nabumetone; tolmetin; etc. Corticosteroids are used to reduce inflammation and suppress activity of the immune system. The most commonly prescribed drug of this type is Prednisone. Chloroquine (Aralen) or hydroxychloroquine (Plaquenil) may also be very useful in some individuals with lupus. They are most often prescribed for skin and joint symptoms of lupus. Azathioprine (Imuran) and cyclophosphamide (Cytoxan) suppress inflammation and tend to suppress the immune system. The side effects of these drugs include anemia, low white blood cell count, and increased risk of infection. Other agents, e.g. methotrexate and cyclosporin are used to control the symptoms of lupus. Both are immunomodulating drugs which have their own side effects. Anticoagulants are employed to prevent blood from clotting rapidly. They range from aspirin at very low dose which prevents platelets from sticking, to heparin/coumadin.

The specification does not disclose the definition of immunomodulating drug. "Modulation is not even a common function as it may include stimulation, suppression, delay, variation, partial antagonism or partial agonism.

The species of immunomodulating drugs disclosed in the instant specification have different structures and mechanisms of action. The specification does not disclose a structure/function relationship for immunomodulating drugs that modulate some aspect of an immune response that alleviate symptoms of lupus and work in tandem with a CD1d-blocking antibody.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any drug that possesses any immunomodulating activity. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 10/30/07 on pages 4-5.

The instant specification discloses that the CD1 blocking agent may be formulated or administered in conjunction with other agents that act to decrease polyclonal B cell activation or otherwise relieve the symptoms of SLE. The specification does not disclose the definition of "immunomodulating," nor does it disclose any other drugs besides the above-mentioned six drugs that are "immunodulating drugs." It is the

Examiner's further position that the genus of an immunomodulating drug is large, for instance, an immunomodulating drug can be an antibody to an immune cell surface receptor, protein, or cytokine, a soluble receptor, a soluble ligand, a cytokine, a small organic or inorganic molecule that mimics or blocks or acts as an antagonist, agonist or partial agonist of an immune system molecule. For example, methotrexate interferes with the production and maintenance of DNA, and has a greater effect on cells that reproduce often such as cancer cells, bone marrow cells, skin cells, and others. In contrast, cyclosporin A antagonizes calcineurin activation, leading to inhibition of NF-AT-supported IL-2 gene expression, and hence to inhibition of calcium induced T cell activation.

With regard to Applicant's argument that a person of ordinary skill in the art can readily determine by way of a drug index, manual, textbook, medical journal, or resources on the internet that a particular drug modulates the immune system, access to said resources does not provide written description for which immunomodulating drugs will act to treat SLE in a human. Identification of a drug by its general functional designation as "immunomodulating" does not provide description for which structure or immunomodulating function correlates with treating SLE in a human.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 15-20 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record).

Amano *et al* teach that the interaction between anti-CD1 T cells and B cells expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG. Amano *et al* further teach that transgenic T cells specific for CD1 (Vβ9/Vα4.4 T cell clone) induce lupus (SLE, an autoimmune disease) when transferred into nude host mice that do not spontaneously develop lupus, that these nude mice develop anti-ds DNA antibodies, proteinuria and ascites, and additionally, that the transgenic T cells could activate wild-type BALB/c B cells via the cross-linking of cell surface CD1 to secrete both IgM and IgG *in vitro*. Amano *et al* teach that T cell proliferation of the said CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11. Amano *et al* teach that

spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (*i.e.*, mice that spontaneously develop disease) is mediated by the CD1^{hi} subset of B cells, "More recent studies have shown that the spontaneous secretion *in vitro* of both IgM and IgG by spleen cells from lupus-prone New Zealand Black/New Zealand White [i.e., NZB/NZW] mice is mediated by the CD1 high subset of B cells" (*i.e.,* that spontaneous antibody secretion in the same disease model used by Applicant is mediated by CD1 positive B cells) (especially second to last paragraph of article). Amano *et al* teach that CD1 by itself or in combination with endogenous antigens appears to be recognized by an autoreactive subset of T cells expresing the NK1.1 surface marker, and that this T cell subset has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the vα14Jα281 associated with Vβ2, Vβ7 or Vβ8 receptors, but that Tcells that express neither the NK1.1 marker nor the Vα14 TCR are able to recognize CD1 on syngeneic antigen presenting cells (especially column 2 on page 1710 at the first paragraph). Amano *et al* teach that CD1d is expressed in both humans and mice (first paragraph).

Amano *et al* do not teach the claimed method of treating pathogenic polyclonal B cell activation or class switching, including that resulting in lupus (SLE), in a human patient, comprising administering a CD1 blocking agent that is an antibody, including a monoclonal antibody.

Kotzin teaches pathogenic IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody-producing B cells (*i.e.,* pathogenic polyclonal B cell activation), a process that mimics a normal T cell dependent response to foreign antigen, involving common mechanisms of affinity maturation, and IgM to IgG class switching (especially first paragraph on page 304). Kotzin teaches that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis of SLE (especially last paragraph on page 303). Kotzin further teaches that T cells are clearly involved in the development of autoantibody production in SLE (especially column 1 on page 303 at the 2nd to the last sentence in column 1).

Zeng *et al* teach T cells with transgenic TCR that recognized CD1 of syngeneic B cells induced lupus with resulting anti-ds DNA autoantibodies, proteinuria and immune complex glomerulonephritis in nude mice that don't spontaneously develop lupus (especially abstract). Zeng *et al* teach anti-CD1 mAbs, including 3C11 (anti-CD1d) (especially materials and methods).

Zeng *et al* teach that severity of disease is associated with the development of the anti-ds DNA autoantibodies and with elevated serum IgG2a as has been observed with hereditary lupus (especially page 534 at the second full paragraph in column 1). Zeng *et al* teach that in hereditary murine lupus, administration of IL-10 worsens the disease and administration of anti-IL-10 antibodies ameliorates the disease likely through regulation of TNF-α secretion since endogenous TNF-α is increased in lupus after the injection of the anti-IL-10 antibodies. Zeng *et al* teach that in hereditary murine lupus, administration of IFN-γ worsens lupus, and the injection of anti-IFN-γ antibodies

ameliorates the disease, and that IFN-γ and IL-10 on one hand, and TNF- α on the other, play opposing roles in regulating the disease (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that both CD4$^+$ and CD4$^-$CD8$^-$ T cells from the spleen of mice with hereditary lupus have been reported to augment the secretion of anti-ds DNA antibodies *in vitro* (especially the last sentence of the paragraph spanning columns 1 and 2 on page 533).

Zeng *et al* teach that SLE inducing cells, *i.e.,* the single positive T cells, secreted large amounts of IFN-γ and little IL-4 (*i.e.,* have a Th1 phenotype), and the SLE preventive cells, i.e., the double negative cells, secreted large amounts of IL-4 (*i.e.,* have a Th2 phenotype) and little IFN- γ and little IL-10 (especially page 525 first column and abstract). Zeng *et al* further teach that introduction of an IL-4 transgene (encodes a Th2 cytokine) into NOD or NZW X C57BL/6 mice prevents SLE. Zeng *et al* teach "It is not surprising that T cells that secrete high levels of IFN- γ and IL-10 and low levels of IL-4 such as the transgenic anti-CD1 CD4$^+$ cells may induce or worsen lupus after activation of their CD1 receptors. One the other hand, the transgenic BM CD4$^-$CD8$^-$ T cells that secrete high levels of IL-4 and low levels of IFN- γ and no IL-10 would have been predicted to ameliorate disease based on their cytokine secretion pattern" (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* also teach "The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical". "...NZB/NZW F1 mice [the same model of spontaneous lupus disclosed by Appellants in the instant specification] lose a subset of T cells..that recognizes CD1 and secretes high levels of IL-4 just before lupus develops. Anti-Vα14 monoclonal antibodies injected into MRL/lpr mice exacerbates the development of lupus, and depletes this T cell subset...The latter subset shows two characteristics (recognition of CD1 and high level secretion of IL-4) with the CD4-CD8- T cell subset in the marrow that prevented lupus in this study (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that "the interaction between anti-CD1 T cells and B cell expressing surface CD1 leads to the activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo." Zeng *et al* teach that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides, *i.e.,* the anti-ds-DNA antibodies for example, in lupus is via T cell recognition of the CD1 molecule (especially page 532 at the first paragraph of the second column).

Blumberg *et al* teach that CD1c is expressed on human B cells in peripheral blood, spleen and tonsil, that CD1a, b and c are expressed on activated monocytes (GM-CSF+/- IL-4), CD1a is expressed on Langerhans cells, CD1a, b and c are expressed on dendritic cells in the dermis and CD1d is expressed in the GI tract on epithelial cells in mice and in humans as well as in other tissues at low levels, and on the majority of human B cells (especially pages 13-15). Blumberg *et al* teach antibodies to the CD1 molecules, including 3C11 (anti-CD1d) and antibodies to CD1a, b and c. Blumberg *et al* further teach that 3C11 blocks the interaction of T cells with CD1d (especially second

paragraph on page 23). Blumberg *et al* teach that 3C11 cross-reacts with human CD1d (specially page 14 at the last paragraph).

Hughes teaches administration of monoclonal blocking antibodies (such as anti-TNFα), including humanized or human antibodies, to patients for a variety of conditions including autoimmune disease. Hughes teaches that the conventional route to derive monoclonal antibodies has been to immunize mice, that these antibodies have widespread applications in research but can trigger immune responses because of the foreign nature of the protein when introduced into humans. Hughes teaches use of humanized or human antibodies avoids such undesirable immune responses (especially page 439).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-CD1d mAb taught by Zeng *et al* or Amano *et al* the anti-CD1d antibodies taught by Blumberg *et al* to block CD1 recognition by T cells as taught by Amano *et al* by administration of antibodies to human patients with SLE, and hence to treat pathogenic polyclonal B cell activation or class switching taught by Kotzin *et al*, including with humanized versions of the said antibodies as taught by Hughes for human patients with autoimmune diseases, and including by the intravenous (IV) route of administration as taught for administration of T cells by Zeng *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to treat pathogenic polyclonal B cell activation or class switching in a patient with SLE with a reasonable certainty of success because:

(1) Amano *et al* teach that interaction between anti-CD1 T cells and B cells that express cell surface CD1 leads to mutual activation of both cell types that results in systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG and that T cell proliferation of the CD1-restricted T cells in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11, that transgenic anti-CD1 T cells can induce SLE with resulting anti-ds DNA antibodies, proteinuria and ascites when transferred into nude host mice that do not spontaneously develop the disease, and that the transgenic T cells could activate wild-type BALB/c B cells via the mechanism of cross-linking cell surface CD1 to secrete both IgM and IgG *in vitro*, and Amano *et al* correlate these teachings with the teaching that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (*i.e.*, mice that spontaneously develop disease) is mediated by the CD1^{hi} subset of B cells;

(2) Kotzin *et al* teach that pathogenic IgG autoantibody production in SLE occurs by clonal expansion of somatically mutated anti-DNA antibody-producing B cells, *i.e.*, by pathogenic polyclonal B cell activation, said activation involving the mechanisms of affinity maturation and IgM to IgG class switching, that T cells are clearly involved in the development of autoantibody production in SLE, and that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis in SLE;

(3) Zeng et al teach that T cells with transgenic TCR that recognize CD1 on syngeneic B cells could induce lupus in nude mice, said mice developing anti-ds-DNA autoantibodies, proteinuria and immune complex glomerluonephritis, that the severity of disease in this experimental system is associated with the anti-ds DNA autoantibodies and with elevated serum IgG2a as it is in mice with hereditary lupus, that T cells expressing the transgenic TCR specific for CD1 regardless of if they were double negative T cells or single positive T cells could induce disease or protect from disease depending upon their cytokine profile, i.e., disease inducing cells secreted large amounts of IFN-γ and little IL-4 whereas disease protective cells secreted large amounts of IL-4 and little IFN-γ or IL-10, that the cytokine secretion patterns of T cells plays a critical role in regulating B cell activation, that these teachings correlate with hereditary murine lupus in that administration of IL-10 or IFN-γ worsens the disease, whereas administration of anti-IFN-γ or anti-IL-10 antibodies ameliorates the disease, that both single positive and double negative T cells from these mice have been reported to augment the secretion of anti-ds DNA autoantibodies in vitro, that introduction of IL-4 transgene into NOD or NZW X C57BL/6 mice prevents SLE, that administration of antiVα14 (i.e., anti-TCR) mAbs to MRL/lpr mice exacerbates the development of lupus because it depletes a subset of T cells that recognize CD1 and secrete a high level of IL-4, that in NZB/NZW mice (i.e., in the same model of spontaneous lupus disclosed by Appellants) said mice lose a subset of T cells with the same characteristics of recognizing CD1 and secreting high levels of IL-4 just before disease develops;

(4) Zeng et al , Amano et al and Blumberg et al teach anti-CD1 mAbs, Blumberg et al further teach CD1 expression on various tissues and cells in the body including B cells and antibodies to CD1, including rat anti-mouse CD1d mAb 3C11 that cross-reacts with human CD1d;

(5) Hughes teaches the administration of monoclonal blocking antibodies such as anti-TNFα to patients to treat a variety of conditions including autoimmune diseases and that it is advantageous when treating human patients to use humanized rodent antibodies to avoid undesirable immune reactions to the foreign nature of the rodent antibodies.

Claim 20 is included in this rejection because the intravenous (iv) route of administration was well known in the art at the time the invention was made and Zeng et al teach intravenous administration of T cells, so it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have injected the antibody/ies via the IV route of administration. The instant claims are included in the instant rejection because the CD1d antibodies taught by Zeng et al or Amano et al would be expected to bind to human CD1d since CD1d of mice or rat would be expected to cross-react with human CD1d due to the high degree of homology between mouse, rat and human CD1d and as taught by Blumberg et al for the rat anti-mouse 3C11 antibody that cross-reacts with human CD1d. Alternately, the value of monoclonal antibodies to proteins was well known in the art at the time the invention was made in terms of specificity, purity and yield, and Blumberg et al teach the human CD1d protein. A routineer would have used the same basic technique for producing

monoclonal antagonist antibodies against human CD1d protein by using an appropriate *in vitro* assay where antagonistic antibodies could be detected. Claims 24-26 are included in this rejection because the art method would be expected to treat SLE, its symptoms and prolong survival.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 10/30/06 on pages 5-7.

The Examiner's position with regard to said arguments and with regard to the Declaration of Dr. Samuel Strober under 37 CFR 1.132 filed on 10/30/07 is as follows:

- Examiner notes that the declarant is the inventor who is arguing his own work is not obvious.

- Applicant's arguments directed to characterization of the mechanism of action are irrelevant, as the instant rejection establishes a reason to administer the antibody as enunciated supra.

- Applicant is arguing the references separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Notwithstanding, the Examiner's position with regard to the following numbered paragraphs in the Declaration of Dr. Samuel Strober under 37 CFR 1.132 filed on 10/30/07 is as follows:

(4) Applicant argues that Zeng does not teach the role of NK T cells in lupus because the experiments (Amano and Zeng) did not study NK T cells, the argument based upon the assertion that the transgenic mouse model used carried the $V\alpha 4.4$ TCR, but that NK T cells express $V\alpha 14$ TCR. Applicant further argues that it would not have been predictable that spontaneous lupus found in NZB/NZW mice that express $V\alpha 14$ TCR (Applicant's model) could be treated with an anti-CD1d antibody.

However, Amano *et al* teach that the $V\alpha 4.4$ T cell clone proliferates in response to CD1-transfected B cells, that this proliferation is blocked by an anti-CD1d mAb, and that this T cell clone can induce lupus. Amano *et al* also teach that this T cell clone can activate normal B cells via cross-linking of cell surface CD1 to secrete both IgM and IgG *in vitro*. Amano *et al* teach that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice that spontaneously develop lupus (and the same model used by Applicant) is mediated by the CD1 high subset of B cells. Amano *et al* teach that CD1 by itself or in combination with endogenous antigens appears to be recognized

by an autoreactive subset of T cells expressing the NK1.1 surface marker, and that this T cell subset has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the $V\alpha14$, but that T cells that express neither NK1.1 marker nor the $V\alpha14$ TCR are able to recognize CD1 on syngeneic antigen presenting cells.

In addition, Zeng *et al* teach a correlation between the cytokine secretion pattern of SLE inducing or protective cells, independent of cell surface phenotype. Zeng *et al* teach "The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical." Zeng *et al* teach loss of a T cell subset that recognizes CD1 and secretes high levels of IL-4 just before lupus develops in NZB/NZW F1 mice (same model as Applicants), and also that in MRL/lpr mice, injection of anti-$V\alpha14$ mAbs exacerbates the development of lupus through depletion of this T cell subset that also shows recognition of CD1 and high level secretion of IL-4. Thus, these combined teachings indicate that the cell surface phenotype, including the TCR usage, is not the indicator of CD1d reactivity and lupus induction, but rather cytokine profile of the T cell is, as enunciated supra in the instant rejection.

(5) Applicant presents evidence that NK T cells, but not conventional T cells, from lupus-prone NZB/W mice can significantly increase secretion of IgM when incubated with B cells, and co-cultures of NK T cells and B cells also produced significantly increased amount of IgG1 and IgG2, as well as increased amounts of IgG anti-dsDNA antibodies. Also, addition of anti-CD1d antibody significantly decreased IgM and IgM anti-dsDNA antibody secretion for marginal zone B cells, and significantly reduced IgG1 secretion.

However, the teaching of the combined references indicates that Amano *et al* recognized that spontaneous secretion of IgM and IgG by splenic B cells from NZB/NZW lupus-prone mice was mediated by the CD1 high subset of B cells and that CD1 appears to be recognized by an autoreactive T cells subset expressing the NK1.1 surface marker. Amano *et al* further recognized that other T cells expressing neither the NK1.1 marker nor the $V\alpha14$ TCR are able to recognize CD1 on antigen presenting cells, that one of these cells expressing a different TCR ($V\alpha4.4$), one that possessed a cytokine secretion profile consistent with lupus disease induction, could activate normal B cells via cross-linking of cell surface CD1 to secrete both IgM and IgG *in vitro*, and that this activation could be blocked by use of anti-CD1d mAb.

(6) Applicant presents evidence extending the finding of (5) to humans. (It is noted by the Examiner that the "Figure 1" cited by Applicant is not of record currently as an attachment to the said declaration.)

However, mouse models of lupus are intended for studying and treating human disease. Amano *et al* as well as Zeng *et al* correlate their teachings using experimental models different from Applicant's with teachings that do use the same experimental model as Applicant's, as well as with teachings relating to hereditary murine SLE and to other models of hereditary murine SLE, for example the MLR/lpr mouse model.

In addition, with respect to Applicant's argument that Dr. Engleman's results suggest that immunoglobulin production in lupus patients' B cells is dysregulated, Kotzin teaches pathogenic IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody producing B cells, that IgG autoantibodies to ds-DNA appear to play a prominant role in the immune complex glomerulonephritis of SLE, and that T cells are clearly involved in the development of autoantibody production in SLE.

One of ordinary skill in the art would have a reasonable expectation of success in producing the claimed method for the reasons enunciated above.

6. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record) as applied to claims 15-20 and 23-26 above, and further in view of the Merck Manual (pages 1317-1321, 16th Edition, 1992, of record).

The combination of Amano *et al* ,Kotzin, Zeng *et al*, Blumberg *et al* and Hughes has been discussed supra, "the combined references".

The "combined references" do not teach the claimed method of treatment of SLE that further comprises administration of a second therapeutic agent for the treatment of SLE, including wherein the second therapeutic agent is an anti-inflammatory drug.

The Merck Manual teaches treatment of SLE with corticosteroid treatment (a class of anti-inflammatory drugs), such as with prednisone, in combination with immunosuppressive agents. The Merck Manual teaches that severe disease with renal damage requires immediate corticosteroid therapy in combination with immunosuppressives, and that in both mild and severe disease, after the inflammatory response is controlled, the minimal dose of corticosteroids and other agents necessary to suppress tissue inflammation must be determined and administered, and that anticoagulant therapy is vital in patients with antiphospholipid antibodies and recurrent thrombosis (especially first three full paragraphs on page 1320, last said full paragraph continuing on to page 1321).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered along with the immunosuppressive agent that is the antibody to CD1 that blocks binding of the TCR to CD1 taught by the "combined references," an anti-inflammatory corticosteroid such as prednisone and/or the anti-coagulant taught by the Merck Manual for treatment of SLE.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more effectively treat SLE by suppressing the immune system by blocking CD1-mediated pathogenic polyclonal B cell activation or class

switching as taught by the "combined references" and to control the inflammatory response using corticosteroid(s) in combination with immunosuppressive agents as taught by the Merck Manual, and to treat with anti-coagulant agents in patients with antiphospholipid antibodies and recurrent thrombosis as is taught by the Merck Manual as being vital for those patients. In addition, motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Section MPEP 2144.07.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 10/20/06 on pages 5-7.

The Examiner's arguments enunciated at item #5 of this Office Action apply herein.

7. Claims 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano et al (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng et al (J. Exp. Med. 1998, 187: 525-536, IDS reference), U.S. Patent No. 6,531,453 B1 (IDS reference), Blumberg et al (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record).

Amano et al teach that the interaction between anti-CD1 T cells and B cells expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo via cross-linking of CD1 to secrete IgM and IgG. Amano et al further teach that transgenic T cells specific for CD1 (Vβ9/Vα4.4 T cell clone) induce lupus (SLE, an autoimmune disease) when transferred into nude host mice that do not spontaneously develop lupus, that these nude mice develop anti-ds DNA antibodies, proteinuria and ascites, and additionally, that the transgenic T cells could activate wild-type BALB/c B cells via the cross-linking of cell surface CD1 to secrete both IgM and IgG in vitro. Amano et al teach that T cell proliferation of the said CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11. Amano et al teach that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (i.e., mice that spontaneously develop disease) is mediated by the CD1^{hi} subset of B cells, "More recent studies have shown that the spontaneous secretion in vitro of both IgM and IgG by spleen cells from lupus-prone New Zealand Black/New Zealand White [i.e., NZB/NZW] mice is mediated by the CD1 high subset of B cells" (i.e., that spontaneous antibody secretion in the same disease model used by Applicant is mediated by CD1 positive B cells) (especially second to last paragraph of article). Amano et al teach that CD1 by itself or in combination with endogenous antigens appears to be recognized by an autoreactive subset of T cells expresing the NK1.1 surface marker, and that this T cell subset has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the Vα14Jα281 associated with Vβ2,

Vβ7 or Vβ8 receptors, but that Tcells that express neither the NK1.1 marker nor the
Vα14 TCR are able to recognize CD1 on syngeneic antigen presenting cells (especially
column 2 on page 1710 at the first paragraph). Amano et al teach that CD1d is
expressed in both humans and mice (first paragraph).
Amano et al do not teach the claimed method of treating pathogenic polyclonal B cell
activation or class switching, including that resulting in lupus (SLE), in a human patient,
comprising administering a CD1 blocking agent that is an antibody, including a
monoclonal antibody.

Kotzin teaches pathogenic IgG autoantibody production in SLE by clonal expansion of
somatically mutated anti-DNA antibody-producing B cells (i.e., pathogenic polyclonal B
cell activation), a process that mimics a normal T cell dependent response to foreign
antigen, involving common mechanisms of affinity maturation, and IgM to IgG class
switching (especially first paragraph on page 304). Kotzin teaches that IgG
autoantibodies to ds-DNA appear to play a prominent role in the immune complex
glomerulonephritis of SLE (especially last paragraph on page 303). Kotzin further
teaches that T cells are clearly involved in the development of autoantibody production
in SLE (especially column 1 on page 303 at the 2nd to the last sentence in column 1).

Zeng et al teach T cells with transgenic TCR that recognized CD1 of syngeneic B cells
induced lupus with resulting anti-ds DNA autoantibodies, proteinuria and immune
complex glomerulonephritis in nude mice that don't spontaneously develop lupus
(especially abstract). Zeng et al teach anti-CD1 mAbs, including 3C11 (anti-CD1d)
(especially materials and methods).

Zeng et al teach that severity of disease is associated with the development of the anti-
ds DNA autoantibodies and with elevated serum IgG2a as has been observed with
hereditary lupus (especially page 534 at the second full paragraph in column 1). Zeng
et al teach that in hereditary murine lupus, administration of IL-10 worsens the disease
and administration of anti-IL-10 antibodies ameliorates the disease likely through
regulation of TNF-α secretion since endogenous TNF-α is increased in lupus after the
injection of the anti-IL-10 antibodies. Zeng et al teach that in hereditary murine lupus,
administration of IFN-γ worsens lupus, and the injection of anti-IFN-γ antibodies
ameliorates the disease, and that IFN-γ and IL-10 on one hand, and TNF- α on the
other, play opposing roles in regulating the disease (especially paragraph spanning
columns 1 and 2 on page 534). Zeng et al teach that both CD4+ and CD4⁻ CD8⁻ T cells
from the spleen of mice with hereditary lupus have been reported to augment the
secretion of anti-ds DNA antibodies in vitro (especially the last sentence of the
paragraph spanning columns 1 and 2 on page 533).

Zeng et al teach that SLE inducing cells, i.e., the single positive T cells, secreted large
amounts of IFN-γ and little IL-4 (i.e., have a Th1 phenotype), and the SLE preventive
cells, i.e., the double negative cells, secreted large amounts of IL-4 (i.e., have a Th2
phenotype) and little IFN- γ and little IL-10 (especially page 525 first column and
abstract). Zeng et al further teach that introduction of an IL-4 transgene (encodes a

Th2 cytokine) into NOD or NZW X C57BL/6 mice prevents SLE. Zeng *et al* teach "It is not surprising that T cells that secrete high levels of IFN- γ and IL-10 and low levels of IL-4 such as the transgenic anti-CD1 CD4^{+} cells may induce or worsen lupus after activation of their CD1 receptors. One the other hand, the transgenic BM CD4^{-}CD8^{-} T cells that secrete high levels of IL-4 and low levels of IFN- γ and no IL-10 would have been predicted to ameliorate disease based on their cytokine secretion pattern" (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* also teach "The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical". "...NZB/NZW F1 mice [the same model of spontaneous lupus disclosed by Appellants in the instant specification] lose a subset of T cells..that recognizes CD1 and secretes high levels of IL-4 just before lupus develops. Anti-Vα14 monoclonal antibodies injected into MRL/lpr mice exacerbates the development of lupus, and depletes this T cell subset...The latter subset shows two characteristics (recognition of CD1 and high level secretion of IL-4) with the CD4-CD8- T cell subset in the marrow that prevented lupus in this study (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that "the interaction between anti-CD1 T cells and B cell expressing surface CD1 leads to the activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo." Zeng *et al* teach that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides, *i.e.,* the anti-ds-DNA antibodies for example, in lupus is via T cell recognition of the CD1 molecule (especially page 532 at the first paragraph of the second column).

U.S. Patent No. 6,531,453 B1 discloses that Vα14 NK T cells were shown to be closely associated with the onset of autoimmune disease, with the Vα14+ NK T cells decreasing prior to the onset of lupus (SLE) in MRL/lpr mice as well as in NZB/NZW mice that spontaneously develop lupus. U.S. Patent No. 6,531,453 B1 discloses that Vα24 is the human homolog of murine Vα14 (especially Background of the invention at lines 39-65). U.S. Patent No. 6,531,453 B1 discloses administering α-glycosylceramides to increase the number of NK T cells, particularly Vα14 NK T cells and Vα24 NK T cells to treat autoimmune diseases such as SLE (column 11 at lines 15-48, column 1 at lines 39-61, examples).

Blumberg *et al* teach that CD1c is expressed on human B cells in peripheral blood, spleen and tonsil, that CD1a, b and c are expressed on activated monocytes (GM-CSF+/- IL-4), CD1a is expressed on Langerhans cells, CD1a, b and c are expressed on dendritic cells in the dermis and CD1d is expressed in the GI tract on epithelial cells in mice and in humans as well as in other tissues at low levels, and on the majority of human B cells (especially pages 13-15). Blumberg *et al* teach antibodies to the CD1 molecules, including 3C11 (anti-CD1d) and antibodies to CD1a, b and c. Blumberg *et al* further teach that 3C11 blocks the interaction of T cells with CD1d (especially second paragraph on page 23). Blumberg *et al* teach that 3C11 cross-reacts with human CD1d (specially page 14 at the last paragraph).

Hughes teaches administration of monoclonal blocking antibodies (such as anti-TNFα), including humanized or human antibodies, to patients for a variety of conditions including autoimmune disease. Hughes teaches that the conventional route to derive monoclonal antibodies has been to immunize mice, that these antibodies have widespread applications in research but can trigger immune responses because of the foreign nature of the protein when introduced into humans. Hughes teaches use of humanized or human antibodies avoids such undesirable immune responses (especially page 439).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-CD1d mAb taught by Zeng *et al* or Amano *et al* or the anti-CD1d antibodies taught by Blumberg *et al* to block CD1 recognition by T cells as taught by Amano *et al* by administration of antibodies to human patients with SLE, and hence to treat pathogenic polyclonal B cell activation or class switching taught by Kotzin *et al*, including with humanized versions of the said antibodies as taught by Hughes for human patients with autoimmune diseases, and including by the intravenous (IV) route of administration as taught for administration of T cells by Zeng *et al*, in order to ameliorate SLE as compensation for the loss of the protective NK T cell subset disclosed by U.S. Patent No. 6,531,453 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to treat pathogenic polyclonal B cell activation or class switching in a patient with SLE with a reasonable certainty of success because:

(1) Amano *et al* teach that interaction between anti-CD1 T cells and B cells that express cell surface CD1 leads to mutual activation of both cell types that results in systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG and that T cell proliferation of the CD1-restricted T cells in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11, that transgenic anti-CD1 T cells can induce SLE with resulting anti-ds DNA antibodies, proteinuria and ascites when transferred into nude host mice that do not spontaneously develop the disease, and that the transgenic T cells could activate wild-type BALB/c B cells via the mechanism of cross-linking cell surface CD1 to secrete both IgM and IgG *in vitro*, and Amano *et al* correlate these teachings with the teaching that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (*i.e.,* mice that spontaneously develop disease) is mediated by the CD1^{hi} subset of B cells;

(2) Kotzin *et al* teach that pathogenic IgG autoantibody production in SLE occurs by clonal expansion of somatically mutated anti-DNA antibody-producing B cells, *i.e.,* by pathogenic polyclonal B cell activation, said activation involving the mechanisms of affinity maturation and IgM to IgG class switching, that T cells are clearly involved in the development of autoantibody production in SLE, and that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis in SLE;

(3) Zeng *et al* teach that T cells with transgenic TCR that recognize CD1 on syngeneic B cells could induce lupus in nude mice, said mice developing anti-ds-DNA

autoantibodies, proteinuria and immune complex glomerluonephritis, that the severity of disease in this experimental system is associated with the anti-ds DNA autoantibodies and with elevated serum IgG2a as it is in mice with hereditary lupus, that T cells expressing the transgenic TCR specific for CD1 regardless of if they were double negative T cells or single positive T cells could induce disease or protect from disease depending upon their cytokine profile, *i.e.,* disease inducing cells secreted large amounts of IFN-γ and little IL-4 whereas disease protective cells secreted large amounts of IL-4 and little IFN- γ or IL-10, that the cytokine secretion patterns of T cells plays a critical role in regulating B cell activation, that these teachings correlate with hereditary murine lupus in that administration of IL-10 or IFN-γ worsens the disease, whereas administration of anti-IFN-γ or anti-IL-10 antibodies ameliorates the disease, that both single positive and double negative T cells from these mice have been reported to augment the secretion of anti-ds DNA autoantibodies *in vitro*, that introduction of IL-4 transgene into NOD or NZW X C57BL/6 mice prevents SLE, that administration of antiVα14 (*i.e.,* anti-TCR) mAbs to MRL/lpr mice exacerbates the development of lupus because it depletes a subset of T cells that recognize CD1 and secrete a high level of IL-4, that in NZB/NZW mice (*i.e.,* in the same model of spontaneous lupus disclosed by Appellants) said mice lose a subset of T cells with the same characteristics of recognizing CD1 and secreting high levels of IL-4 just before disease develops;

(4) Zeng *et al* , Amano *et al* and Blumberg *et al* teach anti-CD1 mAbs, Blumberg *et al* further teach CD1 expression on various tissues and cells in the body including B cells and antibodies to CD1, including rat anti-mouse CD1d mAb 3C11 that cross-reacts with human CD1d;

(5) U.S. Patent No. 6,531,453 B1 discloses that NK T cells are involved in onset of autoimmune disease and teach agents to treat SLE;

(6) Hughes teaches the administration of monoclonal blocking antibodies such as anti-TNFα to patients to treat a variety of conditions including autoimmune diseases and that it is advantageous when treating human patients to use humanized rodent antibodies to avoid undesirable immune reactions to the foreign nature of the rodent antibodies.

Claim 20 is included in this rejection because the intravenous (iv) route of administration was well known in the art at the time the invention was made and Zeng *et al* teach intravenous administration of T cells, so it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have injected the antibody/ies via the IV route of administration. The instant claims are included in the instant rejection because the CD1d antibodies taught by Zeng *et al* or Amano *et al* would be expected to bind to human CD1d since CD1d of mice or rat would be expected to cross-react with human CD1d due to the high degree of homology between mouse, rat and human CD1d and as taught by Blumberg *et al* for the rat anti-mouse 3C11 antibody that cross-reacts with human CD1d. Alternately, the value of monoclonal antibodies to proteins was well known in the art at the time the invention was made, in terms of specificity, purity and yield, and Blumberg *et al* teach the human

CD1d protein. A routineer would have used the same basic technique for producing monoclonal antagonist antibodies against human CD1d protein by using an appropriate *in vitro* assay where antagonistic antibodies could be detected. Claims 24-26 are included in this rejection because the art method would be expected to treat SLE, its symptoms and prolong survival.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered the anti-CD1d mAb with the compound disclosed by U.S. Patent No. 6,531,453 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat SLE because U.S. Patent No. 6,531,453 B1 discloses administering α–glycosylceramides to increase the number of NK T cells, particularly Vα14 NK T cells and Vα24 NK T cells to treat autoimmune diseases such as SLE, wherein the said NK T cells are reduced prior to onset of disease, and Zeng *et al* teach loss of protective cell subsets such as the Vα14+ cells in MRL/lpr mice, and loss of a similar cytokine profile producing cell subset in NZB/NZW mice prior to onset of SLE. In addition, motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their <u>common known purpose</u>. Section MPEP 2144.07.

8. Claims 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), U.S. Patent No. 6,531,453 B1 (IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record), Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record) and the Merck Manual (pages 1317-1321, 16th Edition, 1992, of record).

Amano *et al* teach that the interaction between anti-CD1 T cells and B cells expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG. Amano *et al* further teach that transgenic T cells specific for CD1 (Vβ9/Vα4.4 T cell clone) induce lupus (SLE, an autoimmune disease) when transferred into nude host mice that do not spontaneously develop lupus, that these nude mice develop anti-ds DNA antibodies, proteinuria and ascites, and additionally, that the transgenic T cells could activate wild-type BALB/c B cells via the cross-linking of cell surface CD1 to secrete both IgM and IgG *in vitro*. Amano *et al* teach that T cell proliferation of the said CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11. Amano *et al* teach that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (*i.e.,* mice that spontaneously develop disease) is mediated by the CD1^{hi} subset of B cells, "More recent studies have shown that the spontaneous secretion *in vitro* of both IgM and IgG by spleen cells from lupus-prone New Zealand Black/New Zealand White [i.e., NZB/NZW] mice is mediated by the CD1 high subset of B cells" (*i.e.,* that

spontaneous antibody secretion in the same disease model used by Applicant is mediated by CD1 positive B cells) (especially second to last paragraph of article). Amano *et al* teach that CD1 by itself or in combination with endogenous antigens appears to be recognized by an autoreactive subset of T cells expresing the NK1.1 surface marker, and that this T cell subset has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the $V\alpha14J\alpha281$ associated with $V\beta2$, $V\beta7$ or $V\beta8$ receptors, but that Tcells that express neither the NK1.1 marker nor the $V\alpha14$ TCR are able to recognize CD1 on syngeneic antigen presenting cells (especially column 2 on page 1710 at the first paragraph). Amano *et al* teach that CD1d is expressed in both humans and mice (first paragraph).

Amano *et al* do not teach the claimed method of treating pathogenic polyclonal B cell activation or class switching, including that resulting in lupus (SLE), in a human patient, comprising administering a CD1 blocking agent that is an antibody, including a monoclonal antibody. Amano *et al* do not teach the claimed method of treatment of SLE that further comprises administration of a second therapeutic agent for the treatment of SLE that is an anti-inflammatory drug.

Kotzin teaches pathogenic IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody-producing B cells (*i.e.,* pathogenic polyclonal B cell activation), a process that mimics a normal T cell dependent response to foreign antigen, involving common mechanisms of affinity maturation, and IgM to IgG class switching (especially first paragraph on page 304). Kotzin teaches that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis of SLE (especially last paragraph on page 303). Kotzin further teaches that T cells are clearly involved in the development of autoantibody production in SLE (especially column 1 on page 303 at the 2nd to the last sentence in column 1).

Zeng *et al* teach T cells with transgenic TCR that recognized CD1 of syngeneic B cells induced lupus with resulting anti-ds DNA autoantibodies, proteinuria and immune complex glomerulonephritis in nude mice that don't spontaneously develop lupus (especially abstract). Zeng *et al* teach anti-CD1 mAbs, including 3C11 (anti-CD1d) (especially materials and methods).

Zeng *et al* teach that severity of disease is associated with the development of the anti-ds DNA autoantibodies and with elevated serum IgG2a as has been observed with hereditary lupus (especially page 534 at the second full paragraph in column 1). Zeng *et al* teach that in hereditary murine lupus, administration of IL-10 worsens the disease and administration of anti-IL-10 antibodies ameliorates the disease likely through regulation of TNF-α secretion since endogenous TNF-α is increased in lupus after the injection of the anti-IL-10 antibodies. Zeng *et al* teach that in hereditary murine lupus, administration of IFN-γ worsens lupus, and the injection of anti-IFN-γ antibodies ameliorates the disease, and that IFN-γ and IL-10 on one hand, and TNF-α on the other, play opposing roles in regulating the disease (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that both CD4$^+$ and CD4$^-$CD8$^-$ T cells

from the spleen of mice with hereditary lupus have been reported to augment the secretion of anti-ds DNA antibodies *in vitro* (especially the last sentence of the paragraph spanning columns 1 and 2 on page 533).

Zeng *et al* teach that SLE inducing cells, *i.e.,* the single positive T cells, secreted large amounts of IFN-γ and little IL-4 (*i.e.,* have a Th1 phenotype), and the SLE preventive cells, *i.e.,* the double negative cells, secreted large amounts of IL-4 (*i.e.,* have a Th2 phenotype) and little IFN-γ and little IL-10 (especially page 525 first column and abstract).   Zeng *et al* further teach that introduction of an IL-4 transgene (encodes a Th2 cytokine) into NOD or NZW X C57BL/6 mice prevents SLE. Zeng *et al* teach "It is not surprising that T cells that secrete high levels of IFN-γ and IL-10 and low levels of IL-4 such as the transgenic anti-CD1 CD4$^+$ cells may induce or worsen lupus after activation of their CD1 receptors. One the other hand, the transgenic BM CD4$^-$CD8$^-$ T cells that secrete high levels of IL-4 and low levels of IFN-γ and no IL-10 would have been predicted to ameliorate disease based on their cytokine secretion pattern" (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* also teach "The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical". "...NZB/NZW F1 mice [the same model of spontaneous lupus disclosed by Appellants in the instant specification] lose a subset of T cells..that recognizes CD1 and secretes high levels of IL-4 just before lupus develops. Anti-Vα14 monoclonal antibodies injected into MRL/lpr mice exacerbates the development of lupus, and depletes this T cell subset...The latter subset shows two characteristics (recognition of CD1 and high level secretion of IL-4) with the CD4-CD8- T cell subset in the marrow that prevented lupus in this study (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that "the interaction between anti-CD1 T cells and B cell expressing surface CD1 leads to the activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo." Zeng *et al* teach that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides, *i.e.,* the anti-ds-DNA antibodies for example, in lupus is via T cell recognition of the CD1 molecule (especially page 532 at the first paragraph of the second column).

U.S. Patent No. 6,531,453 B1 discloses that Vα14 NK T cells were shown to be closely associated with the onset of autoimmune disease, with the Vα14+ NK T cells decreasing prior to the onset of lupus (SLE) in MRL/lpr mice as well as in NZB/NZW mice that spontaenously develop lupus. U.S. Patent No. 6,531,453 B1 discloses that Vα24 is the human homolog of murine Vα14 (especially Background of the invention at lines 39-65). U.S. Patent No. 6,531,453 B1 discloses administering α–glycosylceramides to increase the number of NK T cells, particularly Vα14 NK T cells and Vα24 NK T cells to treat autoimmune diseases such as SLE (column 11 at lines 15-48, column 1 at lines 39-61, examples).

Blumberg *et al* teach that CD1c is expressed on human B cells in peripheral blood, spleen and tonsil, that CD1a, b and c are expressed on activated monocytes (GM-CSF+/- IL-4), CD1a is expressed on Langerhans cells, CD1a, b and c are expressed on dendritic cells in the dermis and CD1d is expressed in the GI tract on epithelial cells in mice and in humans as well as in other tissues at low levels, and on the majority of human B cells (especially pages 13-15). Blumberg *et al* teach antibodies to the CD1 molecules, including 3C11 (anti-CD1d) and antibodies to CD1a, b and c. Blumberg *et al* further teach that 3C11 blocks the interaction of T cells with CD1d (especially second paragraph on page 23). Blumberg *et al* teach that 3C11 cross-reacts with human CD1d (specially page 14 at the last paragraph).

Hughes teaches administration of monoclonal blocking antibodies (such as anti-TNFα), including humanized or human antibodies, to patients for a variety of conditions including autoimmune disease. Hughes teaches that the conventional route to derive monoclonal antibodies has been to immunize mice, that these antibodies have widespread applications in research but can trigger immune responses because of the foreign nature of the protein when introduced into humans. Hughes teaches use of humanized or human antibodies avoids such undesirable immune responses (especially page 439).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-CD1d mAb taught by Zeng *et al* or Amano *et al* or the anti-CD1d antibodies taught by Blumberg *et al* to block CD1 recognition by T cells as taught by Amano *et al* by administration of antibodies to human patients with SLE, and hence to treat pathogenic polyclonal B cell activation or class switching taught by Kotzin *et al*, including with humanized versions of the said antibodies as taught by Hughes for human patients with autoimmune diseases, and including by the intravenous (IV) route of administration as taught for administration of T cells by Zeng *et al*, in order to ameliorate SLE as compensation for the loss of the protective NK T cell subset disclosed by U.S. Patent No. 6,531,453 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to treat pathogenic polyclonal B cell activation or class switching in a patient with SLE with a reasonable certainty of success because:

(1) Amano *et al* teach that interaction between anti-CD1 T cells and B cells that express cell surface CD1 leads to mutual activation of both cell types that results in systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG and that T cell proliferation of the CD1-restricted T cells in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11, that transgenic anti-CD1 T cells can induce SLE with resulting anti-ds DNA antibodies, proteinuria and ascites when transferred into nude host mice that do not spontaneously develop the disease, and that the transgenic T cells could activate wild-type BALB/c B cells via the mechanism of cross-linking cell surface CD1 to secrete both IgM and IgG *in vitro*, and Amano *et al* correlate these teachings with the teaching that spontaneous secretion of IgM and IgG

by splenic B cells from lupus-prone NZB/NZW mice (*i.e.*, mice that spontaneously develop disease) is mediated by the CD1^{hi} subset of B cells;

(2) Kotzin *et al* teach that pathogenic IgG autoantibody production in SLE occurs by clonal expansion of somatically mutated anti-DNA antibody-producing B cells, *i.e.*, by pathogenic polyclonal B cell activation, said activation involving the mechanisms of affinity maturation and IgM to IgG class switching, that T cells are clearly involved in the development of autoantibody production in SLE, and that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis in SLE;

(3) Zeng *et al* teach that T cells with transgenic TCR that recognize CD1 on syngeneic B cells could induce lupus in nude mice, said mice developing anti-ds-DNA autoantibodies, proteinuria and immune complex glomerluonephritis, that the severity of disease in this experimental system is associated with the anti-ds DNA autoantibodies and with elevated serum IgG2a as it is in mice with hereditary lupus, that T cells expressing the transgenic TCR specific for CD1 regardless of if they were double negative T cells or single positive T cells could induce disease or protect from disease depending upon their cytokine profile, *i.e.*, disease inducing cells secreted large amounts of IFN-γ and little IL-4 whereas disease protective cells secreted large amounts of IL-4 and little IFN-γ or IL-10, that the cytokine secretion patterns of T cells plays a critical role in regulating B cell activation, that these teachings correlate with hereditary murine lupus in that administration of IL-10 or IFN-γ worsens the disease, whereas administration of anti-IFN-γ or anti-IL-10 antibodies ameliorates the disease, that both single positive and double negative T cells from these mice have been reported to augment the secretion of anti-ds DNA autoantibodies *in vitro*, that introduction of IL-4 transgene into NOD or NZW X C57BL/6 mice prevents SLE, that administration of antiVα14 (*i.e.*, anti-TCR) mAbs to MRL/lpr mice exacerbates the development of lupus because it depletes a subset of T cells that recognize CD1 and secrete a high level of IL-4, that in NZB/NZW mice (*i.e.*, in the same model of spontaneous lupus disclosed by Appellants) said mice lose a subset of T cells with the same characteristics of recognizing CD1 and secreting high levels of IL-4 just before disease develops;

(4) Zeng *et al*, Amano *et al* and Blumberg *et al* teach anti-CD1 mAbs, Blumberg *et al* further teach CD1 expression on various tissues and cells in the body including B cells and antibodies to CD1, including rat anti-mouse CD1d mAb 3C11 that cross-reacts with human CD1d;

(5) U.S. Patent No. 6,531,453 B1 discloses that NK T cells are involved in onset of autoimmune disease and teaches agents for treatment of SLE;

(6) Hughes teaches the administration of monoclonal blocking antibodies such as anti-TNFα to patients to treat a variety of conditions including autoimmune diseases and that it is advantageous when treating human patients to use humanized rodent antibodies to avoid undesirable immune reactions to the foreign nature of the rodent antibodies.

Claim 20 is included in this rejection because the intravenous (iv) route of administration was well known in the art at the time the invention was made and Zeng *et al* teach intravenous administration of T cells, so it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have injected the antibody/ies via the IV route of administration. The instant claims are included in the instant rejection because the CD1d antibodies taught by Zeng *et al* or Amano *et al* would be expected to bind to human CD1d since CD1d of mice or rat would be expected to cross-react with human CD1d due to the high degree of homology between mouse, rat and human CD1d and as taught by Blumberg *et al* for the rat anti-mouse 3C11 antibody that cross-reacts with human CD1d. Alternately, the value of monoclonal antibodies to proteins was well known in the art at the time the invention was made, in terms of specificity, purity and yield, and Blumberg *et al* teach the human CD1d protein. A routineer would have used the same basic technique for producing monoclonal antagonist antibodies against human CD1d protein by using an appropriate *in vitro* assay where antagonistic antibodies could be detected. Claims 24-26 are included in this rejection because the art method would be expected to treat SLE, its symptoms and prolong survival.

The Merck Manual teaches treatment of SLE with corticosteroid treatment (a class of anti-inflammatory drugs), such as with prednisone, in combination with immunosuppressive agents. The Merck Manual teaches that severe disease with renal damage requires immediate corticosteroid therapy in combination with immunosuppressives, and that in both mild and severe disease, after the inflammatory response is controlled, the minimal dose of corticosteroids and other agents necessary to suppress tissue inflammation must be determined and administered, and that anticoagulant therapy is vital in patients with antiphospholipid antibodies and recurrent thrombosis (especially first three full paragraphs on page 1320, last said full paragraph continuing on to page 1321).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered along with the anti-CD1 antibody that blocks binding of the TCR to CD1 an anti-inflammatory corticosteroid such as prednisone and/or the anti-coagulant taught by the Merck Manual for treatment of SLE.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more effectively treat SLE by suppressing the immune system by blocking CD1-mediated pathogenic polyclonal B cell activation or class switching and to control the inflammatory response using corticosteroid(s) in combination with immunosuppressive agents as taught by the Merck Manual, and to treat with anti-coagulant agents in patients with antiphospholipid antibodies and recurrent thrombosis as is taught by the Merck Manual as being vital for those patients. In addition, motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Section MPEP 2144.07.
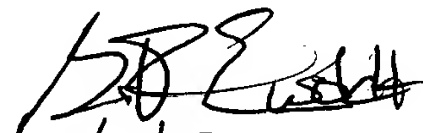
9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 29, 2008

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